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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,341	03/20/2001	Kathy L. Miller	P1780R1	1230

7590 02/20/2004

Attn: Wendy M. Lee
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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,341	MILLER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,11-15,21,25,26,33-37,41,42,57-66,68,69 and 74-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-15,21,25,26,33-37,41,42,57-66,68,69 and 74-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Amendment filed on 2/30/2002.*

DETAILED ACTION

Claims 1, 2, 4-9, 11-15, 21, 25, 26, 33-37, 41, 42, 57-66, 68, 69, 74-80 are pending, and under consideration. Applicant's attention is directed that claim 16 although indicated as pending has been cancelled with the amendment filed on 2/30/2002. Note the attachment. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new ground of rejection.

Specification, Withdrawn

Objection of the specification is withdrawn because applicant supplied the required sequence compliance.

Claim Objections, Withdrawn

The objection of the claims is withdrawn in view of the amendment

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn because applicant argument is persuasive.

Claim Rejections - 35 USC § 102, Withdrawn

The rejection of claims 1, 2, 4- 6, 8, 11-15, 66, 68, 75, 76, 80 under 35 U.S.C. 102(a) as being anticipate by Santos et al (Clin Cancer Res. 1999 Oct;5(10

Suppl):3118s-3123s) is withdraw because applicant antedated instant invention over the art with 131 declaration.

The rejection of claims 1, 2, 4- 6, 8, 12-14, 66, 75, 76, are rejected under 35 U.S.C. 102(a) as being anticipate by Alt et al (FEBS letters, Jul 2 1999, vol. 454, p90-4) is withdraw because applicant antedated instant invention over the art with 131 declaration.

The rejection of claims 57-66, 68, 75-78,and 80 under 35 U.S.C. 102(e) as being anticipated by US Pat 6,066,719 (IDS, May 23, 2000) is withdrawn because the amended base claim 57 is no longer anticipated by the art.

The rejection of claims 21, 25, and 26 under 35 U.S.C. **102(b)** as being anticipated by WO 98/41629 (IDS, 24 September 1998) is withdrawn because the Office is able to meet the burden that DR5 antibody DR5 disclosed at page 36 lines 25 to page 37 lines 5 has more than three antigen binding sites.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of Claim 7 under 35 U.S.C. **103(a)** as being unpatentable over Santos et al (cited supra) as applied to claim 1 and 8 above and further in view of US Pat 6,066,719 (cited supra) is withdrawn because of the 131 declaration, and also

because applicant argument that US Pat 6,066,719 be removed as an art for the reasons given (at pages 16 and 17 of the amendment) is persuasive.

The rejection of Claim 9 under 35 U.S.C. **103(a)** as being unpatentable over of Santos et al above as applied to claims 1 and 8 above and further in view of US Pat 6,066,719 (cited supra) is withdrawn because of the 131 declaration, and also because applicant argument that US Pat 6,066,719 be removed as an art for the reasons given (at pages 16 and 17 of the amendment) is persuasive.

The rejection of Claims 33-42 under 35 U.S.C. **103(a)** as being unpatentable over WO 98/41629 as applied to claims 21-26 above and further in view of either US Pat 6,066,719 (cited supra) or Santos et al above (cited supra) is withdrawn because of the 131 declaration, and also because applicant argument that US Pat 6,066,719 be removed as an art for the reasons given (at pages 16 and 17 of the amendment) is persuasive.

Double Patenting, Withdrawn

The rejection of Claims 57-62, 65 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 6,066,719 is withdrawn in view of the amendment.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 102

Art search is expanded to see the generic claim is allowable.

Claims 1, 2, 4, 8, 9, 12-15, 33, 36, 41, 42, 61-63, 66, 68, 75, 76, 77, 78, 80, 68, 75, and 76 are rejected under 35 U.S.C. 102(b) as being anticipate by Alderson et al (1994, International Immunology, vol. 6, pages 1799-1806).

Claims 1, 2, 4, 8, 9, 12-15, 33, 36, 41, 42, 61-63, 66, 68, 75, 76, 77, 78, 80, 68, 75, and 76 are generic claims, not specifically recites the elected species of "four antigen binding sites". The claims are interpreted as drawn more than three antigen binding sites (claims 1, 2, 66, 68, 75-78) with specified structural and functional characteristic i.e. comprising a polypeptide chain comprises two or more variable domains (claim 4), comprises at least two light chain variable domain polypeptides (claims 8, 33), further comprises a CL domain (claim 9), internalizes faster than a bivalent antibody (claim 12), an agonist antibody (claim 13, 41), induces apoptosis (claim 14, 42), monospecific (claim 15), capable of binding a receptor in the Tumor Necrosis Factor receptor family (claim 33), comprises a dimerization domain (claim 61), said dimerization is a hinge region, an Fc region, a CH3 domain, or CH4 domain (claim 62, said dimerization domain is hinge region (claim 63).

Instant claims read on IgM anti-huFas mAb at page 1800, left column, line 2 of Alderson, which has more than three antigen binding sites because of the vague claim limitations as to the claimed antibody or protein structures in the base claim 1, 33 in light of the prosecution history i.e. the inventor's 131 declaration antedating the art of record, Santos et al and Alt et al. The declaration says that two Fabs are located amino-terminal to an Fc, which indicate that more than three binding sites are result of

dimerization of the two antibody chains with the construct shown at page 9 of the note book shown in inventor's 131 declaration. Note instant specification at Fig. 2E IgM for a pictorial diagram, which shows that IgM with more than three binding sites comprising at least two light chain variable domain polypeptides, further comprises a CL domain, a dimerization domain could be a hinge region, an Fc region, a CH3 domain, or CH4 domain. Alderson et al teach IgM anti-huFas mAb induces apoptosis (note abstract, second paragraph of Introduction at page 1799), binds only one antigen i.e. Fas that belongs to TNF receptor family (note the instant specification at page 8, line 14-32 says that Fas belongs to TNF receptor family). The IgM anti-huFas mAb appears to be an agonist antibody because Fas and the antibody both sends same signal i.e. sending apoptosis signal. Thus, Alderson et al anticipates instant claims 2, 4, 8, 9, 13-15, 33, 36, 41, 42, 61-63, 66, 68, 75, 76, 77, 78, 80, 68, 75, and 76.

As for claims 12, the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the composition of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed composition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed composition is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

If applicant could overcome 102 (b) rejection above, then Claims 1, 2, 4-9, 12-15, 57-66, 68, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9, secondary reference).

The claims are interpreted as drawn to an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) with the recited functions i.e. agonist, internalized faster, induces apoptosis. Note above under 102(b) rejection above for further detail of the instant claims.

The primary reference teaches an engineered antibody with a polypeptide structure of VH-CH1-VH-CH1 at page 1058 (see Fig. 1) and further teaches the engineered antibody $F(ab')_2$ (with more antigen binding sites than Fab) kills cancer cells better (higher antiproliferate activity than Fab), has longer serum half-life than Fab. Note abstract, Figs. 1-5, and Table I and II. The primary reference thus suggests that more binding sites of an engineered antibody might result in a more desirable antibody i.e. higher avidity and prolonged serum half-life, thus less frequent painful injections in clinical use.

The primary reference does not teach Fc or the various recited dimerization domain and does not teach how to make four antigen binding sites.

However, the secondary reference teaches that human Fc region has an effector functions such Fc receptor binding necessary for certain antibody activity (note page 7995 left column, especially the first paragraph of Shu et al) and also teach way to

make multivalent engineered antibody is to add human γ1 Fc region through hinge region such that the polypeptide has region to form dimeric structure (note Fig. 2), and further teach antibody comprising a polypeptide comprising human γ1 Fc region is advantageous because it is immunoglobulins-like and make ex vivo transfection of cells for the delivery of the tumoricidal antibody to the tumor site for gene therapy.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make an antibody comprising a polypeptide structure of VH-CH1-VH-CH1 (as taught by the primary reference which gives two binding sites) linked to Fc since the secondary reference teaches that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized. One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product with reasonable expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life, thereby reducing painful injections and saving money by using less of the product in clinical use.

Claims 1, 2, 4-9, 12-15, 57-66, 68, and 74-78, and claims 21, 25, 26, 33-37, and 41, and 42, are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et

al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9, secondary reference), and further in view of WO 98/41629 (IDS, 24 September 1998).

The claims are interpreted as drawn to an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) with the recited functions i.e. agonist, internalized faster, induces apoptosis, wherein said antibody binds to DR5.

The obviousness of an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) with the recited functions i.e. agonist, internalized faster, induces apoptosis is explained in the 103 (a) above. In this section, only the tertiary reference, WO 98/41629 would be explained. WO 98/41629 teaches antibody to DR5 (see page 36 lines 25 to page 37 lines 5, claims 21, 25, 26) and also teaches agonist antibody useful for treating cancer and other proliferative diseases at page 37 line 5, page 38 lines 31-35.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make an DR-5 binding antibody (useful to treat cancer, cancer treating antibody could generate a lot of revenue) comprising a polypeptide structure of VH-CH1-VH-CH1 (as taught by the primary reference which gives two binding sites) linked to Fc since the secondary reference teaches that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized. One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product with reasonable

expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life DR-5 antibody capable of killing cancer cells, thereby reducing painful injections and saving money by using less of the product in clinical use.

Claims 66, 75, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9, secondary reference), and in further in view of Paprocka et al (1992, Arch Immunol. Ther Exp, vol. 40, pages 223-7, abstract only).

The claim is interpreted as drawn to an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) linked to a cytotoxic agent.

The importance of the primary and secondary references has been explained in the first 103 rejection above.

The tertiary reference teaches that making and using an immunoconjuate linking an antibody to a cytotoxic agent such as ricin for cytotoxic effect is an art-known technique well before the effective filing date of the instant application.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make antibody (useful to treat cancer, cancer treating antibody could generate a lot of revenue) comprising a polypeptide structure of VH-CH1-VH-CH1 linked (as taught by the primary reference which gives

two binding sites) linked to Fc since the secondary reference teaches that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized. One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product by linking to a cytotoxic agent (taught by tertiary reference) with reasonable expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life DR-5 antibody capable of killing cancer cells, thereby reducing painful injections and saving money by using less of the product in clinical use.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
February 8, 2004

LARRY R. HELMS, PH.D
PRIMARY EXAMINER